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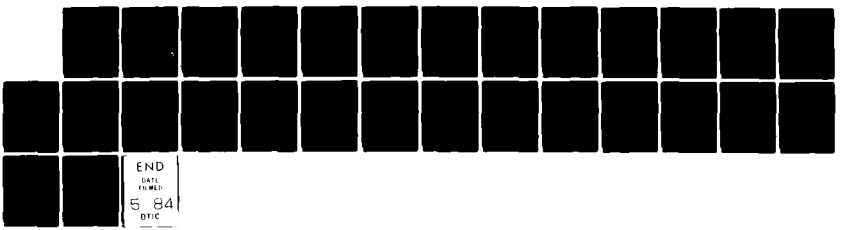

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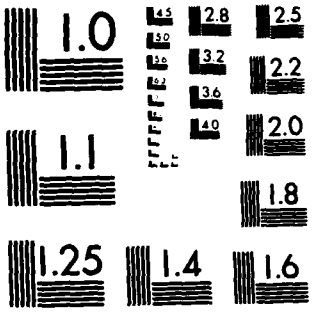

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CARDIO-PULMONARY RESPONSE TO SHOCK

ANNUAL PROGRESS REPORT

February 1981

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Investigations are continuing into the relationship of pulmonary prostaglandin production and systemic organ function. Our study preparations are of pulmonary embolism and/or positive end-expiratory pressure (PEEP) which we believe to be analagous to the microembolism and hyperventilation of severe injury. Both embolism and PEEP lead to the production of thromboxanes (Tx) as well as descreases in cardiac contractility. The latter event can be prevented with Tx antagonists. Tx cause the elaboration of a high molecular

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weight protein fraction which suppresses myocardial Ca^{++}-ATPase and reduces activity of Krebs cycle enzymes in cardiac mitochondria.

During acute thrombocytopenia serotonin (5-HT) infusion was found to protect against petechiae. Antagonists to 5-HT promoted petechiae. Endogenous or exogenously infused prostacyclin (PGI_2) caused a reduction in plasma and increase in platelet 5-HT. Endothelial 5-HT transport was blocked. These findings may underly the ability of PGI_2 to enhance permeability.

Prostacyclin was found to regulate the production of plasminogen activator. This may be one of the mechanism related to the dramatic effectiveness of PGI_2 in reversing the cardiopulmonary abnormalities of pulmonary embolism and in reversing lethal endotoxemia. However, PGI_2 was without benefit in treating acid aspiration, whereas blocking the proaggregatory PGs, effectively reversed the pulmonary edema and the gas exchange abnormalities. Under other circumstances PGI_2 may be hazardous such as during organ perfusion. These studies indicate that PGs are important mediators of critical illness, although their actions may not be predicatable.

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A. Prostaglandin Precursors of Circulating Negative Inotropes

1. Depressed left ventricular function following pulmonary embolism (1)

Pulmonary emboli may impair cardiac performance because of pulmonary hypertension and right ventricular failure. A decrease in left ventricular stroke work (LVSW) may also occur because of a release of humoral factors which reduce cardiac contractility. The latter hypothesis is debated and is the subject of this study. Fourteen dogs were infused with 0.2 g/kg autologous clot, repeated 5 x at 20 min intervals. The rise in pulmonary pressure was related to the fall in stroke volume ($r = -0.55$, $p < 0.001$). Another 19 animals were infused once with 0.5 g/kg clot. A fall in LVSW was observed and was associated with an increased left atrial transmural pressure ($r = -0.55$, $p < 0.01$) and unchanged central venous pressure. Thirty min after embolization platelet counts decreased from 212,000 to 150,000/mm^3 ($p < 0.05$) and the metabolites of prostacyclin and thromboxane A_2 (6-keto-$PGF_{1\alpha}$ and thromboxane B_2) rose ($p < 0.005$, $p < 0.001$). Plasma from embolized animals used to bathe an isolated rat papillary muscle reduced developed tension ($p < 0.01$). Plasma from embolized dogs also decreased Ca^{++}-ATPase activity of a myofibril preparation ($p < 0.001$) obtained from rat cardiac muscle. The decline in Ca^{++}-ATPase was related to the fall in LVSW ($r = 0.57$, $p < 0.001$). Five animals were pretreated with indomethacin prior to embolization with 0.5 g/kg clot, and no decrease in LVSW compared to controls ($p < 0.01$) was observed. Postembolism plasma used to bathe a papillary muscle did not depress contractility ($p < 0.05$) and the same plasma incubated with rat myofibrils did not lower Ca^{++}-ATPase activity ($p < 0.05$) relative to controls. Gel filtration of serum obtained from an embolized animal produced a high molecular weight protein fraction that depressed Ca^{++}-ATPase activity in the myocardial subfractions. These results suggest that pulmonary emboli cause the secretion in plasma of prostaglandins that directly

or indirectly alter myocardial energy production and reduce contractility. It is thought that these results may apply to setting where microemboli form such as severe trauma.

2. Thromboxane mediation of cardio-pulmonary effects of embolism (2)

Humoral factors released during pulmonary embolism may be the cause of several attendant cardiopulmonary abnormalities. This study examines the role of thromboxanes (Tx) following experimental embolism induced with 0.5 g/kg autologous clot in four groups of five dogs: (1) untreated embolized controls; (2) pretreatment with the Tx synthetase inhibitor, imidazole, 25.5 mg/kg·h IV, started 30 min before embolization; (3) pretreatment with the cyclo-oxygenase inhibitor, indomethacin, 5 mg/kg 12 h PO and 1 mg/kg 1 h IV prior to the experiment, (4) treatment with prostacyclin (PGI_2) 100 g/kg·min IV for 1 h, 1 h after embolization. Within 30 min, embolization led to increases of 6-keto-$PGF_{1\alpha}$, the stable metabolite of PGI_2 from 0.11 ± 0.08 (mean ± SD) to 0.33 ± 0.10 ηg/ml ($p < 0.005$) and TxB_2, the stable metabolite of TxA_2 from 0.10 ± 0.04 to 0.38 ± 0.06 ηg/ml ($p < 0.01$). Increases were observed in: physiologic dead space (V_D/V_T) from 46 ± 3 to 58 ± 8% ($p < 0.03$), physiologic shunting ($\dot{Q}_S/\dot{Q}_T$) from 16 ± 4 to 39 ± 9% ($p < 0.01$), pulmonary vascular resistance (PVR) from 2.3 ± 0.6 to 9.2 ± 1.9 mm Hg·min/l ($p < 0.005$) and mean pulmonary arterial pressure from 14 ± 5 to 34 ± 1 mm Hg ($p < 0.001$). Cardiac index (CI) fell from 139 ± 11 to 85 ± 17 ml/kg·min in 4 h ($p < 0.003$). Imidazole pretreatment prevented a rise of TxB_2, but not 6-keto-$PGF_{1\alpha}$; indomethacin blocked both. Both agents maintained V_D/V_T at baseline and limited increases in $\dot{Q}_S/\dot{Q}_T$ and PVR to 31 ± 6% and 6.4 ± 0.6 mm Hg·min/l, respectively. CI was higher after imidazole pretreatment ($p < 0.03$). PGI_2 infusion lowered TxB_2 ($p < 0.005$) and reduced V_D/V_T ($p < 0.03$), $\dot{Q}_S/\dot{Q}_T$ ($p < 0.03$) and PVR ($p < 0.05$) within 30 min. During PGI_2 infusion, CI was similar to the imidazole group. Concentrations of TxB_2 correlated with abnormalities in pulmonary function: V_D/V_T, $r = 0.79$ and $\dot{Q}_S/\dot{Q}_T$, $r = 0.69$ ($p < 0.001$). These results show that a number of cardiopulmonary abnormalities induced by pulmonary

embolism are related to increased circulating levels of thromboxanes.

3. Role of PGs in PEEP-induced negative inotropism (3)

PEEP therapy is used for treatment of hypoxemia in acute respiratory failure. PEEP, however, is limited principally because of its adverse effect on cardiac output (CO) which may be due, in part, to a circulating negative inotropic agent(s). PEEP plasma taken from dogs pretreated with indomethacin (5 mg/kg), aspirin (200 mg/kg), and imidazole (25 mg/kg/h) were tested using an isolated, isometrically contracting rat papillary muscle bioassay. The control dog (untreated) PEEP plasma resulted in a depression of the peak developed tension (Tpd) from 5.45 ± 0.78 to 4.82 ± 0.72 g ($p < 0.001$). PEEP plasma from any of the pretreated dogs did not show depression in Tpd. PEEP increased 6-keto-$PGF_{1\alpha}$ (stable metabolite of PGI_2) levels from 0.076 to 0.130 ng/ml ($p < 0.01$) and increased TxB_2 (Stable metabolite of TxA_2) levels from 0.088 to 0.211 ng/ml ($p < 0.05$). TxB_2 production was inhibited in the pretreated groups, but 6-keto-$PGF_{1\alpha}$ increased only in the imidazole group ($p < 0.01$). The in-vitro addition of indomethacin, aspirin, imidazole or PGI_2 did not cause a depression of Tpd and even at 1 ng/ml TxB_2 caused only minimal Tpd depression. Hence, it is unlikely that TxB_2 is the direct causative agent. In addition, PEEP plasma from an isolated perfused lung lobe did not reduce Tpd. These results suggest that PGs are related to the negative inotropic agent(s) induced by PEEP and that thromboxanes are indirect mediators.

4. PEEP effect on myocardial ATPase activity (4)

Plasma obtained from dogs treated for 30 min with 15 cm H_2O PEEP decreases contractility of rat papillary muscle. This study investigates the action of the humoral negative inotrope on myocardial subfractions. Myofibrils, sarcoplasmic reticulum and sarcolemma were isolated from rat and dog hearts and incubated with non-PEEP and PEEP plasma. PEEP plasma depressed

Ca^{++}-ATPase, but not Mg^{++}-ATPase activity in all rat and dog cardiac subfractions ($p < 0.025$). The decline in Ca^{++}-ATPase activity was significantly correlated with a fall in cardiac output during PEEP. Calcium uptake by the myocardial subfractions was enhanced by PEEP plasma ($p < 0.005$). This event also correlated significantly with a decline in cardiac output and is thought to be an adaptive response to the fall in Ca^{++}-ATPase activity. A fraction (> 160,000 daltons) obtained by gel filtration of PEEP serum depressed Ca^{++}-ATPase activity in myofibril subfractions. No change was observed with serum from non-PEEP dogs. The results indicate that PEEP leads to the secretion of a humoral antagonist that may, by inhibiting myocardial Ca^{++}-ATPase, reduce contractility.

5. PG mediation of unstable hemodynamics during lung perfusion (5)

Pressure breathing alters prostaglandin (PG) metabolism which may in part be responsible for the observed fall in mean arterial blood pressure (MAP) and cardiac output (CO). A support dog was used to perfuse an isolated lung lobe at a fixed flow using a veno-venous circuit. The support dogs in Group I (n=5) and lung lobe donors of Group II were pretreated with indomethacin 5 mg/kg PO. This PG blocker was not used in Group III (n=4). Lobe perfusion with simple mechanical ventilation caused a fall in support dog MAP from 135 ± 9 mm Hg to 122 ± 12 ($p < 0.005$) and CO from 3.33 ± 0.98 L/min to 2.27 ± 0.41 ($p < 0.025$) in Groups II and III. The values of MAP and CO in Group I support dogs were unchanged and were higher than Groups II and III ($p < 0.005, 0.05$). Application of 15 cm H_2O end-expiratory pressure (PEEP) to the lobe was without effect on support dog hemodynamics of any group. Radioimmunoassays of the stable metabolites of prostacyclin (PGI_2) and thromboxane A_2 demonstrated low values of these PGs in Group I compared with II and III. There were no changes in these values during lobe perfusion or application of PEEP to the lobe or support dogs in any group. The results demonstrate

that perfusion of an isolated lobe causes the release of a PG which leads to hemodynamic instability. This PG is not significantly metabolized by the lungs and is not PGI_2.

6. Induction of myocardial damage with nitroprusside, an event unrelated to hypotension (6)

Adverse effects of prostaglandins or nitroprusside (NP) may relate to hypotension and abnormalities in the distribution of blood flow and further with NP to cyanide toxicity. The potential hazards of NP were studied in 16 anesthetized dogs. Four served as non-treated controls while 12 received NP 3 mg/kg IV. Eight of 12 treated dogs were rapidly infused with NP to reduce mean arterial pressure to 40 torr. The pH subsequently fell to 7.1 ($p < 0.01$). Electron microscopy of the myocardium showed swelling and loss of mitochondrial cristae, dilatation of the transverse system and intracellular edema. There were significant decreases in glycogen granules compared with control dogs ($p < 0.005$). The same pH and electron microscopic changes were noted in four dogs given NP at a rate sufficiently slow so mean arterial pressure remained above 80 torr. Plasma cyanide levels in both rapidly and slowly infused animals exceeded 0.5 µg/ml. The data show that NP toxicity is related to total dose and perhaps also to infusion rate. The toxic metabolite may be cyanide. These results have never been seen with PEEP or pulmonary embolism and its is unlikely that prostaglandin effects on cardiac contractility are mediated via hypotension or coronary flow distribution.

B. Control of 5-Hydroxytryptamine (5-HT) Concentrations and Endothelial Cell Function

1. Endothelial cells in homeostasis: pulmonary microvasculature as a model (7,8)

The inaccessibility of the microvasculature has been a major restriction to unravelling the physiological responses of endothelial cells (EC) to changes

in the internal milieu. Information on EC activity, as a barrier and as an homeostatic mechanism, has been collected almost exclusively from in-vivo observations of mesenteric microvessels or from studies on whole organs where observations are then extrapolated to a single vessel or to a microvascular bed. The isolation of intact microvessels and intimal cells, and culture of these tissues, are new techniques with great promise for studying such activities as flux, synthesis and secretion. We have demonstrated that EC, intimal and microvessel, qualitatively share many characteristics such as the specific uptake of serotonin (5-hydroxytryptamine, 5-HT): Quantitatively there may be significant differences between species, analogous organs, arteries and veins and differences may exist even within a given vessel. For example, microvessel endothelial Km and Ki values (imipramine) for 5-HT are 4.7 x 10^{-7}M and 8 x 10^{-7}M respectively; for aortic EC these values were 4.1 x 10^{-7}M and 4 x 10^{-7}M. Data on 5-HT flux and metabolism are provided which suggest that: EC monitor 5-HT blood levels, the amines' metabolism is not a significant factor in ^{14}C-5HT uptake, 5-HT may play a significant role in regulating EC housekeeping activities, such as stimulus-secretion and stimulus-contraction. Two experimental models are presented: 1) 5-HT and thrombocytopenia and 2) alteration of pulmonary EC physiology by ventilation. In the former injections of 5-HT temporarily "protect" a thrombocytopenic hamster, as measured by petechial sensitivity. In the second model both in-vitro and ex-vivo stretching of the lung alveoli by positive end-expiratory pressure can produce a negative inotropic effect. An interpretation is provided, based upon this experimental model, on how alterations in pulmonary EC metabolism may affect cardiac contractions.

2. Saturable carrier mediated and non-facilitative diffusion of serotonin by intimal and microvessel endothelium in vitro (9)

The kinetics of serotonin (5-HT) transport by different in-vitro systems are compared. Microvessel (< 50 μm) endothelial cells (MEC) obtained

from adipose and cardiac muscle tissues, and a ^{3}H-thymidine selected culture of bovine aortic EC are used as substrates. MEC concentration-dependent transport data suggest that at low exogenous 5-HT concentrations uptake is non-linear (apparent Km=5 x 10^{-7}M) and inhibited by 5-HT uptake antagonists (fluoxetine and imipramine), 4^{o}C and selected metabolic inhibitors and analogues. Analysis of transport kinetics at higher concentrations of 5-HT (> 10^{-5}M) indicate a non-saturable, linear mechanism that is pharmacologically less responsive. MEC metabolized 5-HT to 5-hydroxindoloacetic acid by monoamine oxidase (MAO), type A, and depress 5-HT transport.

In marked contrast, a saturable component for 5-HT transport is not detected for ^{3}H-thymidine selected cultured bovine aortic EC. Initial uptake velocities (1 min)(10^{-8}M to 10^{-3}M, 5-HT) indicate that selected intimal EC lack a saturable uptake system. Over a wide range of concentrations (10^{-9}M to 10^{-3}M) uptake as a function of time is linear for 15 min and plateaus between 30-180 min. Pharmacological procedures designed to reveal a carrier mediated transport mechanism produce negative results.

These data indicate that notwithstanding ultrastructural similarities and positive identification with markers, significant transport differences by EC are observed in vitro, which suggest more than one mode of uptake. These contrasting observations may reflect tissue variability but also limitations and quirks of the assay systems. However, there is a commonality of these results and data published elsewhere on 5-HT clearance, in-vivo and in-vitro...that 5-HT uptake is a functional characteristic of all EC.

3. Serotonin transport by isolated adipose capillary endothelium (10)

The transport of serotonin (5-hydroxytryptamine, 5-HT) by endothelial cells was studied in freshly isolated capillary and other microvessel (< 50 μm, inner diameter) endothelium obtained from rat epididymal fat pads. Endothelial cells incubated with (^{3}H) 5-HT transported 60 pmoles (^{3}H) 5-HT/mg

protein at 1 h; an apparent Km of 3×10^{-7}M and a V_{max} of 20 pmoles/mg protein, measured at 15 min, was obtained. Transport of 5-HT (10^{-6}M) was inhibited by ouabain, selected metabolic inhibitors (iodoacetate, 2-4 dinitrophenol and sodium azide), 4^{o}C, tryptamine (10^{-5}M) and the 5-HT antagonists, fluoxetine and imipramine (10^{-5}M and 10^{-4}M, respectively). At concentrations of 5-HT greater than Km value, transport appears to be principally by non-facilitative diffusion rather than by carrier mediated transport.

4. Modes of serotonin transport by intimal and capillary endothelial cells (11)

Serotonin (5-HT) uptake appears to be a functional characteristic of all endothelial cells (EC) in vitro. However, differences in modes of 5-HT transport and responses to substances that affect 5-HT uptake and metabolism have been observed in different preparations. In this report 5-HT uptake kinetics by ^{3}H-thymidine selected bovine aortic EC at confluency are compared with data previously published for non-selected aortic EC in culture and for freshly isolated capillary EC obtained from rat epididymal fat pad. In capillary and cultures of mixed EC 5-HT uptake was observed as a combination of a high affinity carrier mechanism and by non-facilitative diffusion. An apparent Km = 5×10^{-7}M and Vmax = 50 pmol/mg protein at 15 min were calculated for capillary EC. The facilitative mechanism of both tissues was depressed by known antagonists of 5-HT uptake, 4^{o}C, tryptamine and metabolic inhibitors. In contrast, initial uptake velocity measured at 1 min for ^{3}-H-thymidine selected EC does not reveal a detectable saturable component in concentrations tested between 10^{-3}M to 10^{-9}M. Pharmacological experiments designed to detect carrier mediated transport gave no indication that such a system is involved in the concentrations examined. When these selected EC are preincubated with an inhibitor (iproniazid) of monoamine

oxidase at concentrations between 10^{-4}M to 10^{-7}M, no alteration in initial velocity of 5-HT is observed. However, 40 min post-incubation 5-HT uptake was enhanced when compared to control uptake values that had plateaued.

5. Loss of microvascular structural integrity with fluoxetine, a serotonin antagonist (12)

The concept that platelets support microvascular structural integrity is based principally upon the observation that in thrombocytopenia there is an increase in petechial hemorrhages. We and others have shown that platelets leak/release serotonin (5-HT), and the implication of these observations is that platelets deliver to the microvasculature physiologically significant amounts of 5-HT to effect endothelial cell motility, hence microvascular integrity. Exogenous 5-HT injected IP and IV (0.5 mg·100 g^{-1}·h^{-1}) will protect severe thrombocytopenic animals from petechiae, and this is blocked with 5-HT uptake antagonists. This study documents further a putative regulatory role for platelet 5-HT. Single (acute) or multiple (chronic, 21 days) IP injections of the 5-HT uptake antagonist fluoxetine (4.5×10^{-3} mg·100g^{-1}) into hamsters with normal platelet counts increases petechial hemorrhages. In acute experiments, petechial sensitivity is observed at 5 min and 20 min post-injection to be 3.5 x and 6.5 x greater than controls, respectively. Following a single injection of fluoxetine, petechial hemorrhages occur for 1 week, which suggest that the metabolite of fluoxetine is stable and biologically similar to the parent compound. Propanolol (4.5×10^{-3}mg·100g^{-1}) with fluoxetine enhances petechial sensitivity by 20% in normal hamsters.

6. Pericytic venule permeability regulation by platelet serotonin (13)

We have demonstrated a putative regulatory role for serotonin (5-HT) in restoring microvascular structural integrity in cutaneous post-capillary venules in severe thrombocytopenic hamsters. The role of platelets is theorized to deliver-release 5-HT in amounts significantly above plasma levels

to affect a change in endothelial cell motility. To substantiate this theoretical model, hamsters with normal numbers of viable platelets are treated with a wide range of selective inhibitors of 5-HT uptake. Additional studies test the action of these 5-HT antagonists with propanolol and other adenergic receptor blockers. Hamsters received either a single injection (acute response) of the test agents or daily injections for 21 days (chronic). In all experiments 5-HT inhibitors in normal hamsters induced petechial hemorrhaging significantly greater than controls. Petechial sensitivity was observed as early as 5 min post-injection (3.5 x > control). The administration of propanolol to 5-HT inhibitor enhanced petechial sensitivity. A single injection of fluoxetine, believed to be the most specific of all 5-HT uptake antagonists, increased normal hamster sensitivity to petechial formation for as long as 1 week, which indicates that the metabolite of fluoxetine is stable and also has a negative effect on microvascular permeability. A theoretical model based upon 5-HT modulation of regional cytoskeletal constituents is proposed as a mechanism for this pathological symptom associated with thrombocytopenia.

7. Prostacyclin control of plasma and platelet 5-hydroxytryptamine in normal and embolized animals (14)

Several abnormalities in cardiopulmonary function following embolization are thought to be mediated by 5-hydroxytryptamine (5-HT). The proven effectiveness of therapy with prostacyclin (PGI_2) led to this study of the changes in 5-HT concentrations in plasma and platelets with and without prostaglandin treatment. Thirty min after introduction of autologous clot 0.5 g/kg in 19 dogs, plasma 5-HT concentrations rose three-fold ($p < 0.001$) concomitant with a 29% fall in platelet count. A significant correlation ($r = 0.60$, $p < 0.001$) was determined for the observed increase of plasma 5-HT and fall of platelets. Not all 5-HT contained in the lost platelets

was released into, or remained within plasma since whole blood 5-HT levels declined ($p < 0.05$). Platelet 5-HT concentrations were unchanged throughout the 4 h observation period. Infusion of PGI_2 (100 ng/kg·min) for 1 h caused a decrease in 5-HT concentration in mixed venous plasma ($p < 0.005$) and an increase of platelet 5-HT ($p < 0.001$). Similar effects were observed with a PGE_1 infusion (400 ng/kg.min) for 1 h. Platelet 5-HT concentrations remained elevated 2 h after cessation of PGI_2 or PGE_1. In six normal dogs, PGI_2 infusion produced similar results. Plasma 5-HT fell ($p < 0.01$) while platelet levels rose ($p < 0.025$) and clearance of 5-HT by the pulmonary vasculature was inhibited ($p < 0.05$). After embolization, concentrations of 5-HT in mixed venous blood were related to increases in pulmonary vascular resistance ($r = 0.76$, $p < 0.001$), but were poorly correlated with physiologic dead space and were not correlated with physiologic shunting or cardiac output. These results indicate that 5-HT is of secondary importance in mediating the abnormalities of cardiopulmonary function after embolism. Exogenous prostaglandin infusions and perhaps endogenous prostaglandin release during embolization inhibit endothelial cell uptake of 5-HT. High PGI_2 levels enhance platelet uptake resulting in elevated platelet and low plasma concentrations of this amine.

C. Regulatory Roles of Prostacyclin

1. Treatment of pulmonary embolism with prostacyclin (15,16)

In theory prostacyclin (PGI_2) should be useful for the therapy of pulmonary embolism becuase of its ability to inhibit platelet aggregation, dilate the pulmonary vasculature, and stimulate fibrinolytic activity. This hypothesis was tested in 17 dogs who were given autologous blood clot, 0.5 gm/kg IV, labeled with ^{125}I-fibrin. One hour following embolization, mean pulmonary arterial pressure in eight control animals had risen 13.3 mm Hg above the baseline value of 18.1 ± 0.8 mm Hg (mean ± SEM) ($p < 0.005$); physiologic

dead space (V_D/V_T) was elevated ($p < 0.01$) and the physiologic shunt ($\dot{Q}_S/\dot{Q}_T$) rose to 30.4 ± 3.5% from a baseline value of 16.0 ± 1.8% ($p < 0.001$). One hour after embolization, nine dogs were given PGI_2 100 ηg/kg·min IV for 1 hour. Within minutes, mean arterial pressure fell 32 mm Hg ($p < 0.001$) and pulmonary arterial pressure fell 5.2 mm Hg ($p < 0.005$). In 15 min, V_D/V_T and $\dot{Q}_S/\dot{Q}_T$ decreased compared to control values ($p < 0.05$, $p < 0.005$) and in 1 h fibrin degradation products appeared, 18 ± 3 ηg/ml compared with 10 ± 2 ηg/ml in untreated dogs ($p < 0.03$) During this same hour, ^{125}I activity in the lungs decreased 9.8% ($p < 0.005$). In the next hour increased amounts of tracer were found in the urine of PGI_2 treated animals ($p < 0.005$). Afer the PGI_2 infusion was stopped, arterial pressure rose promptly, and V_D/V_T and $\dot{Q}_S/\dot{Q}_T$ continued to improve and were similar to baseline values within another hour. Control animals remained significantly hypoxic compared to the treated group ($p < 0.01$). Cardiac index was well maintained during PGI_2 infusion ($p < 0.01$), but declined immediately after PGI_2 was stopped, and after 2 h cardiac index had fallen by 27 ml/min·kg ($p < 0.001$). This drop was similar to the depressed flow values seen in untreated animals. The results demonstrate that the vasodilating and antiaggregating agent PGI_2 reverses physiologic dead space and shunting associated with pulmonary embolism in 15 to 30 min. Other salutary effects relate to enhanced fibrinolysis and maintenance of cardiac output.

2. Treatment of pulmonary embolism with PEEP and PGE_1 (17)

Prostaglandins are thought to mediate cardiopulmonary responses to pulmonary emboli. This experimental study examines the role of prostaglandin E_1 and 15 cm H_2O positive end-expiratory pressure, a stimulus to prostaglandin synthesis, in the treatment of pulmonary emboli. Injection of 0.5 g/kg ^{125}I labeled autologous clot to anesthetized dogs led to a rise in mean pulmonary arterial pressure to 40 ± 2 torr ($p < 0.001$) as well

as a rise in physiologic dead space and physiologic shunt ($p < 0.025$, $p < 0.005$). There was an increase in thromboxane B_2 ($p < 0.001$) and 6-keto-$PGF_{1\alpha}$ ($p < 0.001$), the stable metabolites of thromboxane A_2 and prostacyclin, respectively. An increase in fibrin degradation products ($p < 0.005$) was also observed. An infusion of 400 ng/kg·min, started 1 h post-embolus and continued for 1 h, decreased mean arterial pressure from 135 to 96 torr ($p < 0.001$). Mean pulmonary arterial pressure declined from 32 to 24 mm Hg ($p < 0.001$); physiologic dead space and shunt rose ($p < 0.05$ and $p < 0.005$) compared with untreated embolized controls. All variables quantitated were indistinguishable from controls after cessation of the prostaglandin E_1 infusion except for mean pulmonary arterial pressure which remained low ($p < 0.01$). End expiratory pressure lowered the physiologic shunt ($p < 0.05$) but also lowered cardiac output ($p < 0.001$). Thromboxane B_2 ($p < 0.05$), 6-keto-$PGF_{1\alpha}$ ($p < 0.05$) and fibrin degradation products ($p < 0.025$) rose with end-expiratory pressure which also produced a 14.2 per cent pulmonary loss of ^{125}I tracer as compared with a 5.3 per cent loss in controls ($p < 0.001$). After removal of end-expiratory pressure, physiologic shunt and mean arterial pressure remained below control values ($p < 0.025$ and $\bar{p} < 0.01$). The results suggest that prostaglandin E_1 leads to non-selective dilatation of the pulmonary vasculature and bronchi, and that end-expiratory pressure may exert some benefit through an increase in prostacyclin secretion.

3. Prostaglandin mediation of pulmonary fibrinolytic activity (18)

The lungs are thought to regulate circulating fibrinolytic activity (FA). Pressure breathing or hyperventilation of the lungs causes the secretion of both FA and prostaglandins. The interrelation between these events is the subject of the present study. Thirteen dogs were anesthetized, intubated, ventilated and subjected to zero cm H_2O end-expiratory pressure (0-EEP) and

then 15 cm H_2O PEEP. After 30 min, pulmonary and systemic arterial blood were drawn. One set of euglobulin fractions was prepared to measure total FA. The other set prepared from plasma from which all plasminogen and plasmin had been removed by affinity chromatography was used to measure non-specific or non-plasmin dependent fibrinolysis. Plasmin-dependent FA was obtained by subtracting non-plasmin activity from total FA, and was expressed as ng fibrin lysed. During 0-EEP the lungs secreted FA. Total FA in systemic arterial blood was 145 ± 57 (mean ± SD) and was higher than pulmonary arterial blood, 87 ± 32 ($p < 0.01$). PEEP increased pulmonary secretion such that systemic arterial levels rose to 238 ± 50 ($p < 0.01$), whereas pulmonary arterial levels rose modestly to 113 ± 43. Increases in plasmin mediated FA accounted for these changes during PEEP; systemic arterial levels were 182 ± 45 and pulmonary arterial values were 76 ± 42 ($p < 0.001$). There were no changes in non-plasmin mediated FA. After giving the cyclo-oxygenase inhibitor indomethacin, 5 mg/kg IV, plasmin mediated activity was almost completely abolished ($p < 0.001$). Further, PEEP failed to stimulate pulmonary FA production. Finally, an infusion of prostacyclin (PGI_2) in four normal anesthetized dogs led to an increase in FA in each animal. These results suggest that pressure breathing and particularly PEEP stimulates the secretion of plasmin mediated FA, and this event is mediated by a prostaglandin such as PGI_2.

4. Plasminogen activator activity of isolated cardiac muscle microvessel endothelial cells (19)

Isolated capillary and other microvessel (< 50 μm) endothelial cells obtained from rat cardiac muscle show plasminogen activator activity that is similar to observations reported for cultured rabbit and bovine aortic and venous intimal endothelium. The extent of plasminogen activator activity is observed to be a function of time and endothelial lysate protein concentration. Microvessel endothelium does not appear to secrete an acid-labile

fibrinolytic inhibitor similar to that reported for cultured intimal cells, which when inactivated at pH 2.7 enhanced plasminogen activator activity.

5. PGI_2 reversal of lethal endotoxemia in dogs (20)

Severe endotoxemia, a condition where microembolization and intravascular coagulation are thought to play important roles, was treated experimentally with prostacyclin (PGI_2). In a study of 24 dogs, eight control animals injected with 1.75 $mg.kg^{-1}$ of endotoxin died within 24 h. Six animals given intravenous aspirin 100 mg/kg, 30 min after endotoxin died. Nine of ten dogs infused with 100 ng $PGI_2 \cdot kg^{-1} \cdot min^{-1}$ for 3 h, given 30 min after the injection of endotoxin survived 24 h ($p < 0.025$). Injection of endotoxin resulted in a: (1) maximal 62% fall in mean arterial pressure (MAP)($p < 0.001$); (2) transient doubling of mean pulmonary arterial pressure (MPAP) ($p < 0.001$); (3) initial 70% drop in cardiac index (CI)($p < 0.001$); (4) decline in blood platelets from 213,700 to 13,700/mm^3 ($p < 0.001$), and white blood cells (WBC) from 7,719 to fewer than 750/mm^3 ($p < 0.001$); (5) depressed urine output ($p < 0.001$); (6) 34% decrease in blood fibrinogen ($p < 0.01$) and an increase in fibrin degradation products (FDPs) above 50 µg/ml ($p < 0.001$); (7) five-fold increase in circulating cathepsin D titer ($p < 0.005$) and (8) increase in blood norepinephrine ($p < 0.005$), dopamine ($p < 0.005$) and epinephrine ($p < 0.001$). Aspirin treatment led to an increase in MAP ($p < 0.001$) and MPAP ($p < 0.005$), but CI, urine flow, platelets, WBC, FDPs and cathepsin D levels remained similar to untreated controls. Following infusion of PGI_2 there was a: (1) prompt increase of CI to baseline levels; (2) late increase in MAP ($p < 0.005$) after the discontinuation of PGI_2 treatment (3) restoration of urine output; (4) increase in circulating platelets to levels still below baseline but above untreated control animals ($p < 0.05$); (5) no effect on circulating WBC levels; (6) fall in FDPs to 11.2 µg/ml ($p < 0.05$); (7) decline in cathepsin D levels to values 60% lower than the untreated

controls ($p < 0.025$); and (8) reduction in plasma norepinephrine levels to baseline at 4 h ($p < 0.005$). Although the mode of PGI_2 action is not clear, it is effective in the treatment of experimental endotoxemia.

6. Thromboxane response to PGI_2 and aspirin treatment in lethal endotoxemia (21)

The role of thromboxanes in mediating abnormalities in cardio-vascular function following endotoxemia was studied in 24 dogs treated with PGI_2 or aspirin. After 1.75 mg/kg endotoxin, a fall in mean arterial pressure (MAP) ($p < 0.001$), cardiac index (CI)($p < 0.001$), platelets and WBC ($p < 0.001$) was observed. Thromboxane B_2 increased from 0.003 ± 0.008 to 0.770 ± 0.180 ng/ml 30 min after endotoxin and 6-keto-$PGF_{1\alpha}$, the stable metabolite of PGI_2 from 0.069 ± 0.015 to 0.451 ± 0.060 ng/ml, respectively ($p < 0.001$). Infusion of PGI_2, 100 ng/kg·min, 30 min after endotoxin for 3 h in 10 dogs was followed by prompt reversal of CI to baseline ($p < 0.001$), a late increase of MAP ($p < 0.005$) and a significant increase in platelet count ($p < 0.05$). Levels of 6-keto-$PGF_{1\alpha}$ increased to 3.30 ± 0.64 ng/ml while TxB_2 decreased to 0.133 ± 0.006 ($p < 0.01$). Intravenous aspirin, 100 mg/kg, 30 min after endotoxin in 6 dogs was followed by a significant increase in MAP ($p < 0.005$), but CI and platelet counts remained low, similar to controls. TxB_2 levels following aspirin decreased to 0.171 ± 0.040 ($p < 0.01$) and 6-keto-$PGF_{1\alpha}$ to 0.165 ± 0.060 ($p < 0.025$). All 8 control and 6 aspirin treated dogs died within 24 h. Nine out of 10 PGI_2 treated dogs survived more than 24 h. It is concluded that TxB_2 is not an important determinant of cardiopulmonary function or survival after severe endotoxemia.

D. Platelet and Leukocyte Mediation of Endothelial Cell Damage: Manipulation With PGs

1. Preservation of platelets and their function in prolonged cardiopulmonary bypass using PGI_2 (22,23)

We studied the effects of PGI_2 with and without heparin on platelet number and function and postoperative bleeding in 22 dogs undergoing two hours of cardiopulmonary bypass (CPB). Data were obtained from four experimental groups: Group I (6 dogs) - normal dose heparin (NDH-1.25 mg/kg); Group II (6 dogs) - low dose heparin (LDH-0.5 mg/kg); Group III (6 dogs) - LDH plus PGI_2 (500 ηg/kg/min); Group IV (4 dogs) - PGI_2 alone (500-1000 ηg/kg/min). On CPB, perfusion pressures averaged 70-90 mm Hg, flows were 1.5-3.0 l/min and the mean hematocrit was 30%. Control platelet counts were 135,000-370,000/mm^3, $\overline{215,000}$. After 30 min on CPB, Group I (NDH) platelets fell to $\overline{36.8\%}$ ± 5.7 (SEM) of control ($p < 0.005$) and Group II (LDH) fell to $\overline{25.6\%}$ ± 7.6 of control ($p < 0.005$); in Group III (LDH + PGI_2) platelet counts fell to only $\overline{74\%}$ ± 7 of control ($p < 0.05$). The improvement between Group III versus Groups I and II was significant ($p < 0.005$). ADP-induced platelet aggregation 60 min post CPB showed poor aggregation in Group I, but near normal aggregation with LDH + PGI_2. Protamine was unnecessary in PGI_2 groups.

Prostacyclin combined with low dose heparin provides adequate anticoagulation on CPB, preserves platelet number and function and is associated with minimal post-CPB bleeding.

2. Adverse effects of PGI_2 on the isolated perfused lung (24)

In an attempt to improve organ function during pump perfusion, the antiaggregating agent PGI_2 was added to whole heparinized blood during perfusion of an isolated left lower lobe of a dog. The volume of the system averaged 1000 ml including a membrane used as a deoxygenator. Flow rates averaged 210/ml·min, being set to achieve an initial mean pulmonary arterial pressure (MPAP) of 15 mm Hg. With flow constant, MPAP in 6 control studies fell, and remained below 10 mm Hg for the 5 h of perfusion. In another 6 studies, PGI_2 was infused at a rate of 1 ηg/min. After 3 h, MPAP rose above 10 mm Hg and at 5 h was 27 mm Hg ($p < 0.005$). Platelet counts in control

lobes fell after 1 h to 45,000/mm^3 ($p < 0.001$) and then gradually rose to 99,000 at 5 h. PGI_2 maintained platelets between 115,000 and 120,000 throughout the study, higher than controls ($p < 0.005$). The physiologic shunt rose from 13 to 24% in controls and to 48% with PGI_2 ($p < 0.005$). Compliance decreased 3 ml/mm Hg in controls and by 6 ml/mm Hg with PGI_2 ($p < 0.001$). Finally, control lobe weights rose 62%. With PGI_2 hemorrhagic edema occured with a 371% weight rise ($p < 0.001$). These results may relate to a PGI_2 induced paralysis of platelet endothelial interaction or to toxic effects of the high doses of infused PGI_2, which might be unique to these in-vitro conditions.

3. Treatment of aspiration pneumonia with ibuprofen and PGI_2 (25)

This study tests the hypothesis that acid aspiration results in pulmonary endothelial cell injury mediated by toxic agents released by platelet and/or leukocyte aggregation. Combinations of the antiaggregating agent PGI_2 and the cyclo-oxygenase inhibitor ibuprofen were given IV to dogs 1 h after the endotracheal instillation of 0.1 N HCl, 3 ml/kg. Four h after aspiration in 6 untreated controls: PaO_2 fell from 91 to 48 mm Hg ($p < 0.001$); the physiologic shunt ($\dot{Q}_S/\dot{Q}_T$) rose from 24% to 45% ($p < 0.005$); physiologic dead space (V_D/V_T) rose from 0.51 to 0.68 ($p < 0.001$); and 108 ± 27 ml ($\bar{x}$ ± SEM) edema fluid drained from the endotracheal tube. The wet/dry lung weight ratio was 9.2, higher than normal 3.6 ($p < 0.001$). Platelets fell 16% and leukocytes rose 149% ($p < 0.03$). PGI_2 was given to 6 dogs in a dose of 100 ng/kg·min for 1 h. V_D/V_T fell ($p < 0.03$), but $\dot{Q}_S/\dot{Q}_T$ was unchanged. Edema fluid accumulated as in controls and the wet/dry ratio was 7.6. Ibuprofen 12.5 mg/kg was given to 6 animals. V_D/V_T fell from 0.66 ± 0.56 ($p < 0.03$), a value indistinguishable from baseline, while $\dot{Q}_S/\dot{Q}_T$ fell from 44% to 30% ($p < 0.005$). Only 20 ml edema fluid appeared and the wet/dry ratio was 4.6, a value lower than untreated controls ($p < 0.005$).

Finally, 6 dogs were treated with ibuprofen 12.5 mg/kg and PGI_2 10 ng/kg·min for 1 h. V_D/V_T and $\dot{Q}_S/\dot{Q}_T$ fell to 0.50 ± 27% ($p < 0.03$, $p < 0.005$). There was no edema and the wet/dry weight ratio was 5.7. Platelets did not fall and leukocyte counts exceeded control values ($p < 0.005$). The finding that ibuprofen and PGI_2 are effective therapy for acid aspiration strongly suggests that platelet and/or leukocyte secretions mediate acid injury to the pulmonary endothelium.

E. Instrument Development

1. A miniaturized chamber for the measure of oxygen consumption (26)

The quantitations of $\dot{V}_{O_2}$ in tissue and cell fractions and alterations in response to various agents is an informative procedure in biological research. Standard $\dot{V}_{O_2}$ chambers require 3-5 ml of test fluid, a relatively large volume for temperature equilibration, and appreciable O_2 may be consumed before stable temperature is obtained. This new chamber, constructed of inexpensive clear plastic requires only a 1 ml volume of test fluid. A standard polarographic oxygen electrode is mounted in a side wall and test fluid is introduced from the bottom. The critical maneuver of rapid removal of bubbles is facilitated by chamber geometry. The funnel-shaped top has a 0.7 mm opening allowing easy escape of bubbles. Samples are introduced within 2 s and within 90 s the temperature can be raised from 22°C to a stable 37°C. A magnetic stir bar insures a well-mixed sample which minimizes concentration and temperature fluctuations at the oxygen electrode. The system has been used to measure, among other things, mitochondrial succinate dehydrogenase oxidative phosphorylation. Individual determinations are completed within 5 min and replicate measurements vary with a standard deviation of ± 2%.

2. A cooling system for prostaglandin infusion (27)

A simple system has been developed for the prolonged infusion of

an iced solution of prostacyclin (PGI_2). In a 24 h period there is a theoretical loss in activity of 6%, while a 5 h infusion leads to a 2% reduction in activity. The stability of the system was demonstrated in six dog experiments where mean arterial pressure was reduced to 58 ± 3.8 torr ($\bar{x}$ ± SEM) over a 5 h period by infusing 500 ηg/kg·min

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